Pulmonary Hypertension: Pharmacological Management Beyond the Lungs

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The speaker has signed a disclosure form and indicated she has no significant financial interest or relationship with the companies or the manufacturer(s) of any commercial product and/or service that will be discussed as part of this presentation.

Session Summary
This presentation will focus on treatment options for persistent pulmonary hypertension of the newborn (PPHN) as well as supportive pharmacological management. Upon completion of this presentation, the attendee will be able to consider many aspects of care for patients with PPHN including sedation and blood pressure management.

Session Objectives
Upon completion of this presentation, the participant will be able to:

- identify drug targets in pulmonary hypertension;
- discuss the mechanisms of action for drugs used to treat pulmonary hypertension;
- review the pharmacologic treatment recommendations for etiologies of pulmonary hypertension that are common in neonates and infants.

References


Pulmonary Hypertension

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Targeted Drug Therapies

Inhaled nitric oxide (iNO)

- Phosphodiesterase-5 (PDE-5) inhibitors
  - Sildenafil
  - Tadalafil

Endothelin receptor antagonists

- Bosentan
- Ambrisentan
- Macitentan

Prostacyclins

- Epoprostenol
- Treprostinil
- Iloprost

Mechanism of action

- Exerts action via soluble guanylate cyclase (sGC) and 2nd messenger, cGMP
- cGMP reduces calcium concentrations and induces smooth muscle cell relaxation → selective pulmonary vasodilation
- Combines with hemoglobin to form methemoglobin → no systemic vasodilation
- Enters ventilated alveoli and causes dilation of neighboring arterioles → improves V/Q mismatch

Effects in animal models of neonatal chronic lung disease

- Stimulates angiogenesis
- Increases alveolarization
- Improves effects of surfactant
- Prevents proliferation of smooth muscle cells

Inhaled Nitric Oxide

Mechanism of action

- Blocks the action of PDE-5 enzyme that breaks down cGMP to inactive GMP
- More cGMP in smooth muscle cells → relaxation and pulmonary vasodilation
- Non-selective pulmonary vasodilator—can cause systemic hypotension
- Ventilation-perfusion mismatch

Drugs

- Sildenafil (Revatio®)
  - Tablet, suspension, IV formulation
  - Data in all ages
- Tadalafil (Adcirca®)
  - Tablet only
  - Dosed once daily, not typically used to treat infants or young toddlers <3 yo

Therapeutic Targets

Inhaled Nitric Oxide

PDE-5 Inhibitors

- Data in all ages
- Dosed once daily, not typically used to treat infants or young toddlers <3 yo

- Vardenafil
- Dosed once daily
Sildenafil Dosing

Metabolized by CYP3A4 and 2C9 in the liver
- Activity increases during first week of life

Oral dosing
- Oral bioavailability ~40% \(\rightarrow\) enteral doses are higher than IV doses
- 0.5-2 mg/kg/dose q6hr to q8hr (PH Guidelines 0.5-1 mg/kg q8hr)
- Start low and titrate (even 0.25-0.3 mg/kg initially)

IV dosing in neonates
- Loading dose of 0.4 mg/kg over 3 hours
- Infusion of 1.6 mg/kg/day \(\times 0.07\) mg/kg/hr
- Intermittent dosing of 0.4 mg/kg over 3 hours (reduce time slowly)

Sildenafil Side Effects

Systemic hypotension
Headache
Dyspepsia
Flushing
Epistaxis
May affect retinal vascularization/cause deterioration of existing retinopathy of prematurity

Original FDA Warning—August 2012

FDA Drug Safety Communication
“The U.S. Food and Drug Administration (FDA) is recommending that Revatio (sildenafil) not be prescribed to children (ages 1 through 17) for pulmonary arterial hypertension (PAH; high pressure in the blood vessels leading to the lungs).

Product Labeling
“Use of Revatio, particularly chronic use, is not recommended in children.”

Deaths as of June 2011

N=35 (26 during treatment; 9 after discontinuation)
- Most associated with disease progression; none attributed to study drug by investigator
- Related to the etiology of PAH
  - 74% had IPAH/HFpEF (33% of study population)
  - 40% in functional class III or IV (15% of the study population)
- Related to disease severity at baseline
  - 74% had baseline value above median for PVR
  - 69% had baseline value above median for mPAP
  - 73% had baseline value above median right atrial pressure
  - 80% had baseline value above median value for NT-proBNP

Revised FDA Warning—March 2014

FDA Drug Safety Communication
“The purpose of the recommendation was to raise awareness of clinical trial results showing a higher risk of mortality in pediatric patients taking a high dose of Revatio when compared to pediatric patients taking a low dose. This recommendation was not intended to suggest that Revatio should never be used in children; however, some health care professionals have interpreted this information as a contraindication, and have refused to prescribe or administer the drug. We recognize there may be situations in which the benefit-risk profile of Revatio may be acceptable in individual children, for example, when other treatment options are limited and Revatio can be used with close monitoring.”
### Endothelin Receptor Antagonists (ERAs)

**Drugs**
- Bosentan (Tracleer®)
- Ambrisentan (Letairis®)
  - Not studied in infants
- Macitentan (Opsumit®)
  - Lacks pediatric data

**Mechanism of action**
- Endothelin is strong vasoconstrictor
- Endothelin-1 (ET-1) is elevated in infants with CDH and PPHN
- Drugs block ET-A and/or ET-B receptors
  - ET-A receptor activation in smooth muscles leads to vasoconstriction via calcium influx
  - ET-B receptor activation in endothelial cells leads to vasodilation via NO release

**REMS Programs**

**Bosentan (Tracleer®)**
- Prescribers and pharmacies must enroll
- ALL patients must enroll
- Baseline and monthly hepatic function and pregnancy tests (if of reproductive potential)
- Prescribers must educate and counsel all patients

**Ambrisentan (Letairis®)**
- Prescribers and pharmacies must enroll
- FEMALE patients must enroll
- Baseline and monthly pregnancy tests (if of reproductive potential)
- No hepatic function tests
- Prescribers must educate and counsel all patients

### Endothelin Receptor Antagonists

**Bosentan**
- Dual antagonist
  - Boxed warning/REMS Program for teratogenicity and hepatic dysfunction
- Side effects:
  - Headache (15%)
  - Edema (11%)
  - Syncope (5%)
  - Abnormal serum aminotransferases (4%)

**Ambrisentan**
- Selective for type A receptor
  - Boxed warning/REMS Program for teratogenicity only
- Side effects:
  - Headache (34%)
  - Peripheral edema (17%)
  - Nasal congestion (6%)
  - Flushing (4%)

### Bosentan Dosing

Weight-based dosing: 1 mg/kg BID increased to 2 mg/kg BID
- Doses used up to 4 mg/kg BID

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Initial Dose</th>
<th>Maintenance Dose</th>
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<tbody>
<tr>
<td>5 to &lt;10 kg</td>
<td>3.5 mg daily</td>
<td>3.5 mg BID</td>
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<tr>
<td>10 to 20 kg</td>
<td>10.25 mg daily</td>
<td>10.25 mg BID</td>
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<tr>
<td>&gt;20 to 40 kg</td>
<td>31.25 mg daily</td>
<td>62.5 mg BID</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>62.5 mg daily</td>
<td>125 mg BID</td>
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</tbody>
</table>

### Prostacyclins (PGI₂)

**Drugs**
- Epoprostenol (Flolan® or Veletri®)
  - Intravenous, inhaled
  - Flolan not stable at room temperature (change every 8 hrs or use ice packs)
- Treprostinil (Remodulin® or Tyvaso®)
  - Intravenous, subcutaneous, inhaled
- Iloprost (Ventavis®)
  - Inhaled

**Mechanism of Action**
- Arachidonic acid metabolite that stimulates adenylyl cyclase in vascular smooth muscle cells → increase in intracellular cAMP → vasodilation of systemic and pulmonary systems
- Systemic administration causes more hypotension than inhaled

### Epoprostenol Dosing

**Continuous infusion**
- Start at 1-2 ng/kg/min and titrate up
- Usual maintenance dose 50-80 ng/kg/min
- Doses >150 ng/kg/min have been used
- Very short half-life of 2-5 minutes; PH crises occur if infusion stopped

**Inhaled**
- Similar dosing range as IV
- Some centers start higher at 10 ng/kg/min and increase by 10-20 ng/kg/min
- Some centers run at 50 ng/kg/min
Treprostinil Dosing
Continuous infusion (IV or subcutaneous)
- Start at 2 ng/kg/min and titrate up
- Usual maintenance dose 50-80 ng/kg/min
- Longer half-life of 4-5 hours; reduced risk of PH crises
- Subcutaneous site pain can limit use
Inhaled
- 1-9 patient activated breaths every 6 hours
- Uses special delivery device—not used in infants

Epoprostenol and Treprostinil Side Effects
Epoprostenol
- Flushing
- Jaw pain
- Foot and bone pain
- Headaches
- Diarrhea
Treprostinil
- Flushing
- Muscle pain
- Headaches
- Diarrhea

Etiologies of Pulmonary Hypertension
Persistent PH of the newborn (PPHN)
Congenital diaphragmatic hernia (CDH)
Bronchopulmonary dysplasia (BPD)
Congenital heart disease (CHD)
Severe acute bronchiolitis syndromes

PPHN Pathophysiology
Rapid drop in PVR should occur at birth to allow for 8x increase in pulmonary blood flow
Decrease in PVR started by increase in oxygen tension, ventilation, and vascular stress
Vasodilation caused by increase in release of NO and prostacyclin from endothelium
PPHN is lack of drop in PVR and increase in pulmonary blood flow and oxygenation

PPHN and General Care
Maintain systemic blood pressure in the normal range for patient’s age
- Treat hypotension with volume and/or medications
- Inotropes such as dopamine, dobutamine, or epi not selective to systemic circulation
- Pulmonary vasoconstriction may occur at high doses
- Supraphysiologic blood pressure not recommended
- Monitor echo to evaluate pulmonary arterial pressure if on high doses of pressors
**Pulmonary Hypertension: Pharmacologic Management Beyond the Lungs**

**Effect of Dopamine in Lambs**

![Graph showing effect of dopamine in lambs.](image)

**Norepinephrine in Infants with PPHN**

18 neonates with PPHN treated with iNO
- Mean gestational age, 37 ± 3 weeks
- Started on norepinephrine at 0.5 mcg/kg/min and titrated up
- Mean systemic artery pressure (SAP) increased from 33 ± 4 to 49 ± 4 mmHg (p<0.05)
- Mean PAP/SAP decreased from 0.98 ± 0.1 to 0.87 ± 0.1 (p<0.001)
- Mean left pulmonary artery blood flow velocity \(V_{LPA}\) increased from 0.30 ± 0.11 to 0.36 ± 0.09 m/s (p<0.05)
- 
- FiO2 decreased from 51 ± 20 to 41 ± 20% (p<0.01)
- Norepinephrine may reduce O₂ requirements and improve lung function in PPHN

**PPHN and General Care**

Exogenous surfactant may be beneficial especially if meconium aspiration syndrome
- Most effective in infants with an oxygenation index of 15-25
- Need for ECMO not reduced in neonates with idiopathic PPHN

Avoid acidosis; Forced alkalosis not recommended
- Alkali infusion associated with higher need for ECMO and oxygen at 28 days
- Sodium bicarbonate may reduce cerebral blood flow

**PPHN and iNO**

Inhaled nitric oxide (iNO) is indicated to reduce the need for extracorporeal membrane oxygenation (ECMO) support in term and near-term infants with PPHN or hypoxic respiratory failure who have an oxygenation index (OI) that exceeds 25 (Class I, Level of Evidence A).
- FDA approved for PPHN in term and near-term neonates
- As many as 40% of infants do not demonstrate improvement or a sustained response to iNO
- Has not been shown to reduce mortality or length of stay
- Doses >20 ppm have no increased benefit; increased risk of methemoglobinemia
- Abrupt discontinuation may lead to rebound PH

**OI at Initiation of iNO**

![Graph showing oxygenation index at initiation of iNO.](image)

**PPHN and iNO in Premature Infants**

iNO can be beneficial for preterm infants with severe hypoxemia that is due primarily to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios (Class IIa, Level of Evidence B).
- Controversial topic with official statements/recommendations from several groups
PPHN and iNO in Premature Infants

National Institutes of Health (NIH) Consensus Statement
- Evidence does not support use in infants <34 weeks requiring respiratory support
- May have benefit in certain situations (e.g., pulmonary hypertension or hypoplasia)
- Communicate evidence and risks with families
- Future research needed
- Hospitals, clinicians, and industry should avoid marketing iNO to infants <34 weeks

Intravenous Sildenafil

PPHN and Sildenafil

Sildenafil is a reasonable adjunctive therapy for infants with PPHN who are refractory to iNO, especially with an OI that exceeds 25 (Class IIa, Level of Evidence B).
- Randomized blinded study of neonates with severe PPHN and OI >25
  - 6 infants received placebo; 1 survived
  - 7 infants received enteral sildenafil; 6 survived
- Open-label dose escalation trial of neonates >34 weeks gestation with PPHN and OI>15
  - 36 neonates started on IV sildenafil (29 already receiving iNO)
  - Improvement in OI (38.7 to 15.3, p=0.0002) after 4 hours in infants who received higher dose groups
  - Recommended doses: 0.4 mg/kg over 3 hours then infusion at 1.6 mg/kg/DAY
  - 35/36 neonates survived, 1 required ECMO
  - Sildenafil stopped due to adverse events in 4 neonates

PPHN and Inhaled Prostacyclins

Inhaled prostacyclin (PGI2) analogs may be considered as adjunctive therapy for infants with PPHN who are refractory to iNO and have an OI that exceeds 25 (Class IIb, Level of Evidence B).
- Risk of hypotension or ventilation-perfusion mismatch with systemic administration
- Inhaled administration of epoprostenol (Flolan®) more common than IV in neonates
  - High pH 10.2 - 10.8
  - Newer diluent for Flolan® has even higher pH: 11.7 - 12.3
PPHN and Inhaled Prostacyclins—Case Reports

Four term infants with PPHN and systemic or suprasystemic pulmonary artery pressure

- All infants treated with oscillator, INO, and inotropes (dopamine, dobutamine, and milrinone)
- Average OI of 29 ± 5
- Intravenous epoprostenol was aerosolized to give 50 ng/kg/min
- After 1 hr: mean PaO₂ increased from 57 ± 6 to 100 ± 27 (p= 0.06)
- After 2 hrs: mean OI decreased from 29 ± 5 to 19 ± 7 (p<0.05)
- One infant only had transient improvement; died 6 days later
- 3 infants survived; received inhaled epoprostenol from 7-18 days

Efficacy of IV Epoprostenol in Infants

Prospective study of 8 infants with PPHN (34-42 weeks gestational age)

- After 72 hours of prostacyclin: mean PaP dropped from 68.6 ± 6.5 mmHg to 49.2 ± 3.5 mmHg (p=0.0005)
- All 8 survived without ECMO; 2 infants (25%) developed BPD

Case report of epoprostenol in 1 infant with CDH

- Combined with sildenafil and INO
- Transient benefit and eventual treatment failure

Epoprostenol in 1 infant (41 weeks gestational age) with PPHN

- Infant on INO at 60 ppm with OI=50 at 72 hours of age
- IV epoprostenol started and OI 13.6 after 18 hours; both drugs weaned off

Safety of IV Epoprostenol & Treprostinil in Infants

Reviewed the use of PGI₂ in 36 patients

- Median age at initiation of treatment: 44 days (range, 1-359 days)
- All infants were intubated
- Other therapies at initiation: INO, sildenafil, diuretics, milrinone, and inotropes
- 34 initiated on epoprostenol and 2 on treprostinil

Etiology of PH

- Idiopathic PH; PPHN; PH associated with CDH, CHD, bronchiolitis, or chronic lung disease

Dosing

- Final infusion rates ranged from 4-50 ng/kg/min for epoprostenol and 11-105 ng/kg/min for treprostinil

PPhN and IV Milrinone

IV milrinone is reasonable in infants with PPHN and signs of left ventricular (LV) dysfunction (Class IIb; Level of Evidence B).

- Improves cardiac function through lusitropy and inotropy
- Reduces pulmonary venous hypertension
- Results in pulmonary and systemic vasodilation
Milrinone

CDH and iNO

*iNO therapy can be used to improve oxygenation in infants with CDH and severe PH, but should be used cautiously in subjects with LV dysfunction (Class IIa, Level of Evidence B).*

- May not be as helpful in infants with PH associated with CDH as in those with PPHTN
- Differences may be due to cardiac pathology—left ventricular dysfunction and hypoplasia
- Limit use to infants with suprasystemic PVR, right-to-left atrial shunting, and pre-ductal hypoxemia
- Milrinone may be better choice to improve LV function and pulmonary venous hypertension

Patients with CDH and iNO

Neonatal Inhaled Nitric Oxide Study (NINOS) Group
- Randomized, controlled, multi-center trial
- 53 infants with CDH >34 weeks and < 14 days of age
- Infants randomized to 20 ppm of iNO or 100% oxygen
- Oxygenation index ~45 at initiation in both groups
- No difference in combined endpoint of ECMO use/death between treatment and control
- ECMO use higher in iNO treated group

CDH and Prostaglandin E₁ (Alprostadil)

*Prostaglandin E₁ may be considered to maintain patency of the duc tus arteriosus and to improve cardiac output in infants with CDH and suprasystemic levels of PH or RV failure to improve cardiac output (Class IIb, Level of Evidence C).*

- Increases right-to-left ductal shunting

BPD and Pulmonary Hypertension

PAH-targeted therapy can be useful for infants with BPD and PH on optimal treatment of underlying respiratory and cardiac disease (Class IIa, Level of Evidence C).

- PH occurs in 25-37% of infants with BPD
- Medications include INO, sildenafil, endothelin-receptor antagonists, and calcium channel blockers

Treatment with INO can be effective for infants with established BPD and symptomatic PH (Class IIa, Level of Evidence C).

- Open label study of 16 infants (23-29 weeks gestation) aged 1-7 months
- After 72 hours, 11 infants had ≥5% reduction in FIO₂
- 4/11 infants who responded weaned from mechanical ventilation
- All non-responders continued on mechanical ventilation or died

Treatment of Postop PH in Children with CHD

General postoperative strategies for avoiding PHCs, including the avoidance of hypoxia, acidosis, and agitation, should be used in children at high risk for PHCs (Class I, Level of Evidence B).

Induction of alkalosis can be useful for treatment of PHCs (Class IIa, Level of Evidence C).

- Brief use of hyperventilation or sodium bicarbonate
- Prolonged alkalosis may cause injury
- Pulmonary vasodilation to sodium bicarb may not be permanent
Treatment of Postop PH in Children with CHD

Administration of opiates, sedatives, and muscle relaxers is recommended for reducing postoperative stress response and the risk for or severity of PHCs (Class I, Level of Evidence B).

- Fentanyl reduces stress response in neonates from surgery
- Continuous fentanyl and muscle relaxers recommended early-postoperatively
- Additional fentanyl before suctioning to reduce risk of PHCs

IN addition to conventional postoperative care, iNO or inhaled PGI$_2$ should be used as the initial therapy for PHCs and right-sided heart failure (Class I, Level of Evidence B).

- iNO post-op reduced PHCs
- No effect on time to extubation with iNO
- Sildenafil shown to help prevent rebound PH after iNO stopped

Treatment of CHD and Postoperative PH

In patients with PHCs, inotropic/pressor therapy should be used to avoid RV ischemia caused by systemic hypotension (Class I, Level of Evidence B).

- Milrinone, levosimendan (not available in US) or nesiritide may be useful
- Cause pulmonary vasodilation and improve cardiac output
- Only if patient can tolerate systemic vasodilation
- Vasopressin may be useful
- Pulmonary vasodilator and systemic vasoconstrictor

Anticoagulation

Not recommended in young children with PAH due to concerns regarding bleeding complications

Recommended in these patient groups

- Idiopathic or heritable PH
- Low cardiac output syndrome
- Long-term indwelling catheters
- Hypercoagulable states

Mechanisms of acute RV failure and pulmonary hypertensive crisis
**Prevention of PH Crises/Acute RV Failure**

Avoid hypoxia
- Hypoxia causes vasoconstriction
- Hyperoxia causes vasodilation

Avoid acidosis
- Acidosis causes pulmonary vasoconstriction
- Alkalosis causes pulmonary vasodilation
- Alkalosis via hyperventilation or sodium bicarbonate infusion not recommended
- Prolonged alkalosis may affect vascular tone, cerebral vasoconstriction and neurodevelopmental markers

Avoid agitation
- Morphine causes histamine release → can increase PVR and PAP; decrease SVR
- Fentanyl preferred due to absence of histamine release and less effect on PAP and PVR

**PH Crises/Acute RV Failure**

Induction of alkalosis can treat PHCs

Opiates, sedatives, and paralytics recommended for reducing postop stress response and risk of PHCs
- Fentanyl may be preferred over morphine

iNO and/or inhaled PGI₂ initial treatment for PHCs and RV failure

**Sildenafil**
- Use to prevent rebound PH in patients with increase in PAP with withdrawal of iNO and patients who require iNO restarted despite weaning

**Preventive Care**

Respiratory syncytial virus prophylaxis—Palivizumab
- <1 year of age
- Moderate to severe pulmonary hypertension

Influenza and pneumococcal vaccinations